Appendix 1: Computational framework [posted as supplied by author]

Burden of disease estimation

The expected loss in (quality-adjusted) life-years $L(a_0)$ due to vaccine-preventable HPV infection for a male aged a_0 years was calculated as the sum over both HPV types 16 and 18 (henceforth denoted types *i* = 1, 2) and all HPV-associated tumour sites *j*:

$$L(a_0) = \sum_i \sum_j L_{ij}(a_0)$$

Our calculation is an approximation as the risk of tumours caused by different types are actually competing risks. This approximation greatly facilitates computation, and is valid because the type-specific tumour risks are small.

We defined $f_j(a;a_0)$ as the population-averaged risk of having cancer *j* diagnosed at age *a* conditional on having survived to age a_0 and $\ell_j(a)$ as the (quality-adjusted) life-years lost if cancer *j* is diagnosed at age *a*. The proportion of cancer cases at site *j* that can be attributed to HPV type *i* is represented by p_{ij}, for which we assumed no association with age. From these definitions, it follows that the expected loss $L_{ij}(a_0)$ per vaccine-preventable HPV type *i* at tumour site *j* for a male aged a_0 years may be calculated as:

$$L_{ij}(a_0) = p_{ij} \int_{a \geq a_0} f_j(a;a_0)\ell_j(a)\,\mathrm{d}a$$

The number of (quality-adjusted) life-years lost if cancer *j* is diagnosed at age *a* was calculated from the modified life expectancy at age *a*, as follows:

$$\ell_j(a) = e_a - \int_{t \geq 0} S_j(t;t_0 = a) U_j(t)\,\mathrm{d}t$$
$$= \frac{1}{S_0(a)} \int_{t \geq 0} [S_0(a+t) - S_0(a) S_j(t;t_0 = a) U_j(t)]\,\mathrm{d}t$$

Here, e_a is the conditional expected future lifetime assuming survival to age *a*, S_0 is the standard survival function in the absence of cancer *j*, $S_j(t;t_0 = a)$ is the survival function if HPV-associated cancer *j* is diagnosed at age *a*, and $U_j(t)$ is the adjusted quality of life per life-year after cancer *j* has been diagnosed. Quality of life adjustment depends on the time *t* elapsed since cancer diagnosis, but is not assumed to depend on the age at diagnosis. Disease-specific survival functions were obtained as:

$$S_j(t;t_0 = a) = \exp[-\Lambda_0(t;t_0 = a) - \Lambda_j(t) \exp(\beta_0^j + \mathbf{1}_{\{A\}} \beta_1^j)]$$

Here, $\Lambda_0(t;t_0 = a)$ denotes the cumulative baseline hazard function from age *a*, with $\Lambda_0(t) = -\log S_0(t)$, $\Lambda_j(t)$ denotes the cumulative excess hazard of dying from cancer *j* in a reference age group, β_0^j is the hazard ratio of HPV-positive cancers at tumour site *j* relative to cases not related to HPV, $\mathbf{1}_{\{A\}}$ is the indicator function specifying membership of age *a* to age group *A*, and β_1^j is the hazard ratio if cancer *j* is diagnosed in age group *A* other than the reference age group. The reader is referred to appendix 2 for details on the estimation of the expected loss in quality-adjusted life-years.

Evaluation of vaccination strategies

We evaluated the impact of female-only and gender-neutral vaccination specifically for a cohort of 12-year-old boys, the same age at which girls are currently being vaccinated in the Netherlands. Our first aim was to estimate the number of (quality-adjusted) life-years gained from preventing future cancers in this male cohort as a result of the existing female-only vaccination programme. We assumed that the reduced transmission of

HPV16 and -18 due to female vaccination will lower the HPV-associated cancer risk among males, but will not affect the excess risk of HPV-associated cancers among MSM.

To obtain a measure for the excess burden of HPV-associated cancers among MSM relative to heterosexual males, we calculated the population attributable fraction (PAF) of male homosexuality for the relevant tumour sites. In general, the PAF is a comparison of incidence (either rate or number of cases, as in our example) under the observed pattern of exposure with the incidence under a counterfactual pattern in which exposure is entirely absent from the population.[1] Here, the observed pattern of exposure is a male population with a proportion MSM, and the counterfactual pattern is a completely heterosexual male population. By letting ρ denote the prevalence of MSM in the adult male population, and θ_j the relative risk for cancer *j* among MSM relative to heterosexual males, the corresponding PAF for cancer *j* is:

$$PAF_j = \frac{\rho(\theta_j - 1)}{\rho(\theta_j - 1) + 1}$$

Next, we estimated the lifetime risk reduction $g_i(a_0; c)$ for HPV type *i* infection among heterosexual males aged a_0 years conditional on a constant vaccine coverage *c* among 12-year-old girls, and projected this reduction onto the burden of HPV-associated cancers that are not attributable to male homosexuality, i.e. the cancer-specific fraction 1 – PAF. Infection risk estimates were derived from a dynamic model for heterosexual HPV transmission, that has also been used to assess the long-term impact of female vaccination on cervical disease in the Netherlands.[2,3] The reduction $g_i(a_0; c)$ was obtained by comparing the lifetime risk for HPV type *i* infection in a null scenario without vaccination to the lifetime risk in a scenario with constant vaccine coverage *c* among 12-year-old girls.

The expected per-capita gain in (quality-adjusted) life-years in a cohort of 12-year-old boys $F(a_0 = 12; c)$ obtained from vaccinating 12-year-old girls was calculated as:

$$F(a_0 = 12; c) = \sum_i g_i(a_0 = 12; c) \sum_j (1 - PAF_j) L_{ij}(a_0 = 12)$$

This calculation assumes an absence of vaccine-preventable HPV type *i* infections at all relevant tumour sites *j* at the cohort starting age a_0 years, which can only be safely assumed prior to sexual debut. The use of lifetime infection risk reduction as a proxy for the lifetime cancer risk reduction was motivated by two observations: first, lifetime infection risk is dominated by infection risks at relatively young age, i.e. between adolescence and midlife when rates of sexual partner change are highest; and second, reductions in infection risk are almost entirely restricted to this age range, as the reduction becomes negligible from age 40 years onward (fig A in appendix 3). We used the HPV16 and -18 lifetime infection risk at the post-vaccination equilibrium to inform the reduction $g_i(a_0 = 12; c)$ as current cohorts of 12-year-old boys are expected to experience an infection risk that approximates the male infection risk at the equilibrium under female-only vaccination (fig B in appendix 3). We specifically report on the health gains for men derived from female vaccination at 60% vaccine coverage, the current uptake among 12-year-old girls in the Netherlands, and at 90% vaccine coverage, the target level in the Dutch national immunization programme.[4]

Our second aim was to estimate the incremental benefit of vaccinating 12-year-old boys once particular vaccine coverage among 12-year-old girls had been achieved. To simplify our calculations, we assumed that vaccine uptake is not associated with sexual behaviour, and that vaccinated males are equally likely to form sexual partnerships with vaccinated as with non-vaccinated females. Under these assumptions, the direct benefit of the male vaccinee can be obtained by projecting vaccine efficacy directly onto the remaining loss in (quality-adjusted) life-years after subtracting herd protection from female vaccination. Following previous definitions, the gain in (quality-adjusted) life-years for 12-year-old boys conditional on a female vaccine coverage *c* was calculated as:

$$G(a_0 = 12; c) = \nu\left[L(a_0 = 12) - F(a_0 = 12; c)\right]$$

Here, ν denotes the prophylactic vaccine efficacy, which is assumed equal for both HPV vaccine types. Note that the gain in vaccinated boys does not depend on vaccine uptake among boys as we estimate the direct benefit for the vaccinees.

In sensitivity analyses, we also considered indirect effects of male vaccination with regard to prevention of HPV-related cancers in men. To this end, we calculated the incremental lifetime risk reduction $h_i(a_0;c_m;c)$ for HPV type *i* infection in heterosexual males aged a_0 years under the assumption a fraction c_m of 12-year-old boys would be vaccinated in a scenario with constant vaccine coverage *c* in 12-year-old girls. We used the lifetime infection risk in the new equilibrium under gender-neutral vaccination to inform $h_i(a_0;c_m;c)$ but it should be noted that this equilibrium is achieved some time after inclusion of boys in the vaccination programme (Fig C in appendix 3). Initial cohorts of vaccine-eligible boys will not yet experience such large reductions in infection risk, the discrepancy being especially large if vaccine uptake among boys is high. The extra herd protection among non-vaccinated heterosexual males resulting from vaccinating 12-year-old girls and boys with respective vaccine coverage *c* and c_m, relative to a scenario of vaccinating girls only, was obtained by projecting the type-specific incremental risk reductions $h_i(a_0;c_m;c)$ onto the remaining loss in (quality-adjusted) life-years per HPV type *i* after subtracting herd protection from female vaccination. Let the latter be denoted by $M_i(a_0=12;c)$, with:

$$M_i(a_0=12;c)=\sum_j\left[1-g_i(a_0=12;c)(1-PAF_j)\right]L_{ij}(a_0=12)$$

The incremental gain in (quality-adjusted) life-years among non-vaccinated 12-year-old boys obtained from other males was subsequently calculated as:

$$H(a_0=12;c_m;c)=\sum_i h_i(a_0=12;c_m;c)\,M_i(a_0=12;c)$$

Eventual herd immunity in non-vaccinated MSM could be incorporated if the lifetime risk reduction $h_{MSM,i}(a_0;c_m)$ for HPV type *i* infection among male homosexuals, conditional on vaccine coverage c_m among 12-year-old boys, were known. This reduction should be projected onto the burden of HPV-associated cancers that are attributable to male homosexuality, as follows:

$$H_{MSM}(a_0=12;c_m)=\sum_i h_{MSM,i}(a_0=12;c_m)\sum_j PAF_j\, L_{ij}(a_0=12)$$

Note that $H(a_0=12;c_m;c)$ and $H_{MSM}(a_0=12;c_m)$ only apply to non-vaccinated boys, whereas $G(a_0=12;c)$ applies to vaccinated boys instead. The overall gain in (quality-adjusted) life-years for a cohort of 12-year-old boys, with a fraction c_m vaccinated, was finally defined as:

$$G_{cohort}(a_0=12;c_m;c)=cG(a_0=12;c)+(1-c\nu)\left[H(a_0=12;c_m;c)+H_{MSM}(a_0=12;c_m)\right]$$

Our model of heterosexual HPV transmission does not allow for quantification of herd immunity in non-vaccinated MSM resulting from a reduced homosexual transmission. Hence, we omitted the term $H_{MSM}(a_0=12;c_m)$ from the latter equation and acknowledge that the total benefit of male vaccination remains underestimated in our calculations. Note however that we expect $h_{MSM,i}(a_0;c_m)$ to be smaller than $h_i(a_0;c_m;c)$ because the reduction in homosexual transmission will be smaller than the incremental reduction in heterosexual transmission at a given male vaccine coverage. For example, vaccinating 50 percent of boys on top of 90 percent of girls is expected to halt heterosexual transmission of HPV16 and -18 (fig A in appendix 3), but this will likely not suffice to halt homosexual transmission.

SUPPLEMENTARY REFERENCES

1. Rothman KJ, Greenland S. Modern Epidemiology [2nd ed]. Lippincott-Raven, 1998.
2. Bogaards JA, Xiridou M, Coupé VM, Meijer CJ, Wallinga J, Berkhof J. Model-based estimation of viral transmissibility and infection-induced resistance from the age-dependent prevalence of infection for 14 high-risk types of human papillomavirus. *Am J Epidemiol* 2010;171:817-25.
3. Bogaards JA, Coupé VM, Xiridou M, Meijer CJ, Wallinga J, Berkhof J. Long-term impact of human papillomavirus vaccination on infection rates, cervical abnormalities, and cancer incidence. *Epidemiology* 2011;22:505-15.
4. de Melker H, Kenter G, van Rossum T, Conyn-van Spaendonck M. Developments in HPV vaccination [in Dutch]. *Ned Tijdschr Geneeskd* 2012;156:A5410.